

(19)



Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number:

**0 253 506
A1**

(12)

EUROPEAN PATENT APPLICATION

(21) Application number: 87305294.8

(51) Int. Cl. 4: A61L 27/00, C04B 38/06

(22) Date of filing: 15.06.87

(30) Priority: 16.06.86 JP 139846/86

(43) Date of publication of application:
20.01.88 Bulletin 88/03

(84) Designated Contracting States:
DE FR GB IT NL

(71) Applicant: KUREHA KAGAKU KOGYO
KABUSHIKI KAISHA
9-11 Horidome-cho 1-chome Nihonbashi
Chuo-ku
Tokyo 103(JP)

(72) Inventor: Nagai, Hiroshi
4-2-47, Fujimu-cho
Chofu-shi Tokyo(JP)

(74) Representative: Lawrence, Peter Robin
Broughton et al
GILL JENNINGS & EVERY 53-64 Chancery
Lane
London WC2A 1HN(GB)

(54) Implant material and process for producing the same.

(57) A highly strong implant material having continuous passages in a dimensional direction, which is a ceramic material comprising hydroxyapatite and is useful as the substitutive material for bones in the fields of surgery and orthopaedics or the filling material in the cavities of bones in the fields of dentistry and oral surgery is disclosed. Also disclosed is a process in which a body is made of alternate layers of particulate hydroxyapatite and nets of organic polymer, the body is press-moulded, then heated to gasify the net and then fired to produce the new ceramic material.

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IMPLANT MATERIAL AND PROCESS FOR PRODUCING THE SAME

The present invention relates to a novel ceramic material of hydroxyapatite, which is useful as the substitutive material for bones in the fields of surgery and orthopaedics or the filling material in the cavities of bones in the fields of dentistry and oral surgery and a process for producing the novel ceramic material. The ceramic material of hydroxyapatite of the present invention is a ceramic material of hydroxyapatite with continuous and two-dimensional pores, which is excellent in an affinity with and an adhesion to the newly formed bones by virtue of having continuous passages in two-dimensional directions, and has a strength necessary as a substitutive material for bones by virtue of having a layer of highly compressed ceramic.

Hydroxyapatite has been known as one of the constituent components of bones and teeth and because it is excellent in an affinity with a living body and is not injurious to a living body, hydroxyapatite has been expected as the prosthetic material in a lost part of a cavity of a bone following a fracture or the removal of bone tumour, and many studies have been carried out concerning the medical use of hydroxyapatite.

Of the studies, porous hydroxyapatite has been proposed as the material which accelerates an activation of the osteophagocytes and the osteoanagenesis cells and is easily able to be fixed into one body with a bone of the host. For instance, in Japanese patent application Laid-Open (KOKAI) No. 57-119,745/1982, a three-dimensionally porous prosthetic material of the mean diameter of the internally continuous openings of 0.1 to 8mm and of the porosity of not less than 60% has been disclosed and in Japanese Patent Application Laid-Open (KOKAI) No. 60-16,879/1985, a porous material in which the internal openings of a diameter of 1 to 600 μm have been connected to outside space of capillary vessels of a diameter of 1 to 30 μm has been proposed.

However, when a material is made porous, the reduction of its strength is generally unavoidable and such a material is not necessarily satisfiable in the point of porous hydroxyapatite which is excellent in an affinity with a living body and has a practically reliable mechanical strength.

As a result of the present inventor's earnest studies, while considering the above situations, for developing an implant material which is excellent in an affinity with and an adhesion to the newly formed bone and is high in strength, it has been found by the present inventors that the porous hydroxyapatite which is obtained by a specific pro-

cess and has the two-dimensional and continuous pores (passages) is in conformity with the object of the present invention and on the basis of their findings, the present invention has been attained.

The object of the present invention lies in providing a novel ceramic material comprising hydroxyapatite, which is useful as the substitutive material for bones in the fields of surgery and orthopaedics or the filling material in the cavities of bones in the field of dentistry and oral surgery. Moreover, the object of the present invention lies in providing a process for producing the ceramic material of hydroxyapatite - having desirable properties.

According to present invention a novel ceramic material of hydroxyapatite is characterised in that the material has continuous passages in two-dimensional directions. The passages may also be referred to as pores.

The ceramic material of hydroxyapatite, can have excellent affinity for and adhesion to the newly formed bone and can retain the necessary strength as the substitutive material for bones.

In the present invention there is also provided a process for producing a ceramic material in which a body is formed by arranging alternate layers of particulate hydroxyapatite and nets of organic polymer fibres in a mould, heating the body at a temperature in the range 200 to 500°C to heat decompose and gasify the net, and then firing the body at a temperature in the range 900 to 1400°C.

The ceramic material of hydroxyapatite may be produced by press-moulding a laminated body comprising a layer of net made of natural or synthetic fibres and a layer of natural or synthetic powdery hydroxyapatite, by heat-decomposing the net made of fibres and then by sintering the press-moulded, laminated body under an ordinary pressure or an applied pressure. The material produced is characterised in having the continuous passages therein, is excellent in an affinity with and an adhesion to newly formed bones and has a sufficient strength as the substitutive material for bones in the fields of surgery and orthopaedics or the filling material in the cavities of bones in the field of dentistry and oral surgery.

The process may be carried out by alternately piling up the unfired or partially fired powdery hydroxyapatite (i.e. particulate hydroxyapatite) and nets made of natural or synthetic fibres, preparing a piled and moulded body from the piled body, for example while using a press-moulding method,

heat-decomposing and gasifying the net at the temperature of 200 to 500°C and then firing the piled and moulded body at a temperature of 900 to 1400°C.

As the hydroxyapatite, synthetic or natural hydroxyapatite or the fired product thereof and a mixture thereof may be exemplified.

The synthetic hydroxyapatite can be produced by any publicly known method and for instance, it is synthesized by a dry synthetic method wherein $\text{Ca}_3(\text{PO}_4)_2$ and an excess of CaCO_3 are brought into reaction in a flow of steam of a high temperature of 900 to 1300°C as described in "Ceramics", Vol. 10 (7), page 461 (1975), a method wherein an emulsion of fine-particle calcium hydroxide and an aqueous solution of phosphoric acid are brought into reaction under a high speed agitation (refer to Japanese patent application Laid-Open (KOKAI) No. 56-45, 814/1981) or a wet synthetic method wherein an aqueous solution of $\text{Ca}(\text{NO}_3)_2$ and an aqueous solution of $\text{NH}_4\text{H}_2\text{PO}_4$ are brought into reaction under a NH_4OH -alkaline state (refer to "Angewandte Chemie", 67, 327 (1955)).

The natural hydroxyapatite can be obtained from natural bones as the raw material. For instance, cow's bones are calcined at a temperature around 800°C to remove organic materials therefrom and the natural hydroxyapatite is obtained. When necessary, the hydroxyapatite can be the material containing β -wittlockite or a different element such as fluorine, iron, etc.

The diameter of powdery hydroxyapatite particle should not be larger than 1000 μm taking into consideration of the processability in moulding and the handling thereof, and is preferably 0.01 to 200 μm , and more preferably 0.1 to 100 μm .

The powdery hydroxyapatite of the above particle size is available, for instance, by a method wherein coarse particles of hydroxyapatite are pulverized in the presence of an organic solvent with a ball mill. The pulverizing method is profitable compared to the ordinary method in the point that the time for pulverizing can be shortened and in case of necessity, the step of classification or the step of freeze-drying, which is necessary when water is used, can be omitted. As the organic solvent, it is preferable to use a solvent of a relatively low boiling point such as acetone, hexane and alcohols.

The fabricated or moulded net used in the present invention is used to form the two-dimensional and continuous passages by heat-decomposition and gasification (disappearance) of the net material by sintering the piled and moulded body comprising hydroxyapatite and the net and accordingly, it is preferably that the nets are made of non heat-shrinkable organic polymer so that the piled and moulded body is not deformed in the step of sintering. As the organic polymer, thermosetting

synthetic polymer such as polyimide, triethylene glycol dimethacrylate and polyester, thermoplastic synthetic polymer such as polymethyl methacrylate, polystyrene, polyvinyl acetate and polypropylene polyethylene or natural polymer such as cellulose and collagen may be exemplified.

Although the diameter of the organic polymer can be properly selected according to the desired diameter of the passages in the ceramic material, it is preferable to use monofilaments of a diameter in the range of 20 to 2000 μm from the view point of the affinity of pores to a living body (invasion of the fibrous tissue and ability to forming bones).

The size of the aperture of the fabricated or moulded net comprising the organic polymer can be properly selected according to the desired porosity of the ceramic material and the size is generally in the range of 0.5 to 5 mm, preferably 1 to 2 mm. The net may be moulded from polymer or otherwise fabricated from polymer fibres.

When piling the fabricated or moulded net and hydroxyapatite, hydroxyapatite is used in the dry powdery state or after being slurried with water or an organic solvent. After piling up the fabricated or moulded net and hydroxyapatite, the piled body is generally subjected to press-moulding to obtain the piled and moulded body of the desired shape. For moulding the piled body by a press-moulding method, the press method at ordinary temperature, the hot-press method or the rubber press method may be used singly or may be used in combination.

The ceramic material of the present invention can be produced by firing the piled and moulded body at a temperature of 900 to 1400°C. Although the firing may be carried out without applying a pressure, the firing can be carried out also applying a pressure of 300 to 1000 kg/cm^2 , for instance, using a hot-press.

When the ceramic material of the present invention, which is prepared by the process mentioned above, is applied to the use for the artificial bone of the artificial jawbone, judging from the stand point of mechanical strength and biocompatibility, the ceramic material having the porosity of 20 to 90% and the continuous openings of a mean diameter of 50 to 1500 μm in the two-dimensional directions is suitable.

In the case of applying the ceramic material of the present invention, for instance, to the jawbone, the ceramic material is to be placed so that the porous part of the material contacts with the natural bone and the compact part of the material contacts with the gum.

Besides, the ceramic material of the present invention, which is calcined as a piled and moulded body of a shape of concentric centres instead of a flat-type, has continuous and two-dimensional pores along the periphery of each circles. Such a body of the ceramic material is particularly useful as artificial bone.

The ceramic material of the present invention can be used as the filling material in the cavities of the bones in a form of powder not only for use as the surgical implant material.

The present invention will be described more in detail while referring to the non-limitative Examples as follows:

EXAMPLE 1:

The filtered and dried cake of synthetic hydroxyapatite obtained by bringing an emulsion of fine-particle calcium hydroxide and an aqueous solution of phosphoric acid into reaction under a high speed agitation was pulverized into particles of a diameter of about 5 μm in a mortar, and the obtained particles were supplied into a ball mill. After adding acetone in an amount of 3 times by volume of the particles into the ball mill, the particles were further pulverized to obtain a fine-particle material of a mean diameter of 25 μm .

Separately, six pieces of a moulded net of synthetic fibre of polymethyl methacrylate (diameter of the filament of 1 mm) of an aperture of 2 mm were cut from the whole net in the size of the metal mould (100 mm in length and 50 mm in width) for use as the female mould of the openings of the ceramic material. In this case, the ceramic material with continuous pores was set up to be 40% in porosity and 10 mm in thickness.

In a metal mould, one of the six pieces of net was placed and 15.7 g of the fine-particle hydroxyapatite were placed on the net evenly.

The remaining pieces of the net were piled up with the hydroxyapatite in the same manner as described above. Thereafter, the piled body in the metal mould was press-moulded under a pressure of 200 kg/cm^2 and then, the press-mould body was further press-moulded under a pressure of 100 kg/cm^2 with a rubber press. The further press-moulded body was heated at 400°C for five hours to decompose and gasify the net of polymethyl methacrylate and then fired for one hour at 1200°C.

Thus, a sintered body of hydroxyapatite having uniform, continuous and two-dimensional passages (pores) of a mean diameter of 1000 μm and a porosity of 40% was obtained. The flexural strength of the sintered body was 150 kg/cm^2 .

EXAMPLE 2:

After provisionally firing the coarse particles of hydroxyapatite of the filtered and dried cake described in Example 1 for 3 hours at 800°C, the obtained coarse particles were pulverized into fine particle of a diameter of not more than 25 μm in the same manner as in Example 1.

Separately, 12 pieces of the moulded net of polystyrene (diameter of the filament of 500 μm) of an aperture of 2 mm were cut from the whole net in the size of 100 mm in length and 50 mm in width for use as the female mould of the openings of the ceramic material with continuous pores was set up to be 40% in porosity and 10 mm in thickness as in Example 1.

The amount of the fine-particle hydroxyapatite placed in the metal mould was set up to 7.8 g/net, and hydroxyapatite and the nets were piled up in the same manner as in Example 1.

Thereafter, the piled materials in the metal mould were press-moulded under a pressure of 200 kg/cm^2 and further press-moulded by a rubber press of a pressure of 1000 kg/cm^2 , and then, the further moulded body was heated for five hours at 400°C to decompose and gasify the polyethylene net and then fired for one hour at a temperature of 1350°C.

Thus, a sintered body of hydroxyapatite having the uniform, continuous and two-dimensional passages of a mean diameter of 500 μm and a porosity of 40% was obtained. The flexural strength of the sintered body was 210 kg/cm^2 in the average.

EXAMPLE 3:

After cut-processing the sintered bodies of hydroxyapatite obtained in Examples 1 and 2 into a semi-cylindrical shape of a size of 10 mm in length, 20 mm in width and 10 mm in height and sterilizing the cut bodies with a high pressure steam according to an ordinary method, the sterilized bodies were implanted into the mandibular base of a shepherd dog of a body weight of 35 kg.

After 6 months of the implantation, the shepherd dog was sacrificed and the pathological specimen of the hard tissues of the implanted region was prepared and examined. As the results, according to the findings of X-ray photograph of the hard tissue, it was found that the formation of bones reached to the central part of implanted body. On the other hand, according to the finding of the de-calcium specimen, the invasion of the fibrous tissue and the blood vessels into the newly formed bone was confirmed.

According to the above-mentioned findings, it was recognized that the ceramic material of the present invention having continuous and two-dimensional pores can be used clinically as a reinforcing material to defect parts in the mandibula.

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Claims

1. A ceramic material comprising hydroxyapatite, characterized in that said ceramic material has continuous passages in the two-dimensional directions.

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2. A ceramic material of hydroxyapatite according to claim 1, wherein said continuous passages have a mean diameter of from 50 to 1500 μm .

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3. A ceramic material according to claim 1 or claim 2 which has a porosity of from 20 to 90%.

4. A process for producing a ceramic material in which a body is formed by arranging alternate layers of particulate hydroxyapatite and nets of organic polymer fibres in a mould, heating the body at a temperature in the range 200 to 500°C to heat decompose and gasify the net, and then firing the body at a temperature in the range 900 to 1400°C.

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5. A process according to claim 4 in which the nets are formed of non-heat shrinkable organic polymer fibres.

6. A process according to claim 5, wherein the organic polymer comprises polyimide, triethylene glycol dimethacrylate, polyester, polymethyl methacrylate, polystyrene, polyvinyl acetate, polypropylene, cellulose or collagen.

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7. A process according to any of claims 4 to 6 in which the fibres have diameters in the range 20 to 2000 microns.

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8. A process according to any of claims 4 to 7 in which the body is formed of substantially flat layers or is cylindrical and formed of tubes of concentric layers.

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9. A process according to any of claims 4 to 8 in which the body is press moulded after the layers are arranged.

10. An implant for humans or animals comprising a ceramic material which is a material according to any of claims 1 to 3 and/or is the product of a process according to any of claims 4 to 9.

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DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl. 4)
X	GB-A-2 078 696 (MITSUBISHI) * Claim 1 * ---	1-3	A 61 L 27/00 C 04 B 38/04
D, X	FR-A-2 548 661 (SUMITOMO) * Page 7, lines 20-32; page 8, lines 20-25; page 11, lines 14-37; page 12, lines 1-5; claims 1-7, 16, 17, 22, 23 * -----	1-10	
			TECHNICAL FIELDS SEARCHED (Int. Cl. 4)
			A 61 L 27/00
The present search report has been drawn up for all claims			
Place of search THE HAGUE		Date of completion of the search 06-11-1987	Examiner PELTRE CHR.
CATEGORY OF CITED DOCUMENTS			
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document	